PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

BC

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 319/06 — A1

(11) International Publication Number: WO 92/06968

(43) International Publication Date: 30 April 1992 (30.04.92)

(21) International Application Number: PCT/US91/06697

(22) International Filing Date: 11 September 1991 (11.09.91)

(30) Priority data:
599,521 17 October 1990 (17.10.90) US

(71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

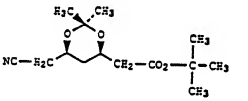
(72) Inventors: MILLAR, Alan ; 14173 Foxtrail Drive, Holland, MI 49424 (US). BUTLER, Donald, Eugene ; 1005 Central Avenue, Holland, MI 49423 (US).

(74) Agents: TINNEY, Francis, J.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.

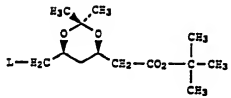
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU+.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

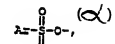
(54) Title: PROCESS FOR THE SYNTHESIS OF (4R-CIS)-1,1-DIMETHYLETHYL-6-CYANOMETHYL-2,2-DIMETHYL-1,3-DIOXANE-4-ACETATE



(I)



(V)



(α)

(57) Abstract

A process for the preparation of the compound of formula (I) which comprises treating a compound of formula (V) wherein L is halogen or (α), wherein Ar is aryl, with a compound of the formula (VI): M-CN. A second aspect of the present invention is a novel intermediate of formula (V).

+ See back of page

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**ES**	Spain	**MG**	Madagascar
AU	Australia	**FI**	Finland	**ML**	Mali
BB	Barbados	**FR**	France	**MN**	Mongolia
BE	Belgium	**GA**	Gabon	**MR**	Mauritania
BF	Burkina Faso	**GB**	United Kingdom	**MW**	Malawi
BG	Bulgaria	**GN**	Guinea	**NL**	Netherlands
BJ	Benin	**GR**	Greece	**NO**	Norway
BR	Brazil	**HU**	Hungary	**PL**	Poland
CA	Canada	**IT**	Italy	**RO**	Romania
CF	Central African Republic	**JP**	Japan	**SD**	Sudan
CG	Congo	**KP**	Democratic People's Republic of Korea	**SE**	Sweden
CH	Switzerland			**SN**	Senegal
CI	Côte d'Ivoire	**KR**	Republic of Korea	**SU+**	Soviet Union
CM	Cameroon	**LI**	Liechtenstein	**TD**	Chad
CS	Czechoslovakia	**LK**	Sri Lanka	**TG**	Togo
DE	Germany	**LU**	Luxembourg	**US**	United States of America
DK	Denmark	**MC**	Monaco		

PROCESS FOR THE SYNTHESIS OF (4R-CIS)-1,1-DIMETHYLETHYL-6-CYANOMETHYL-2,2-DIMETHYL-1,3-DIOXANE-4-ACETATE

BACKGROUND OF THE INVENTION

(4R-Cis)-1,1-dimethylethyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-acetate is a key intermediate in the preparation of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl]-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide or the salt of the hydroxy acid, [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1), corresponding to the opened lactone ring of the aforementioned compound described in United States Patents 4,647,576 and 4,681,893, which are herein incorporated by reference. The aforementioned compound is useful as an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and is thus useful as a hypolipidemic and hypocholesterolemic agent.

(4R-Cis)-1,1-dimethylethyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate may be, in turn, prepared from (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate.

A synthetic procedure for preparing (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate is disclosed in copending United States Patent Application Serial Number 303,733. The aforementioned procedure involves a linear synthetic route involving 10 steps, including a low temperature (-85°C to -95°C) reaction carried out under carefully controlled conditions. The reaction involves

reduction of a hydroxy ketone with sodium borohydride and a trialkylborane. Although this reaction provides the target compound in high enantiomeric excess, it is difficult to conduct on a large-scale and employs expensive reagents which are difficult to handle.

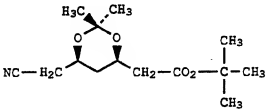
The displacement of sulfonates and halides by cyanide is well known in the art. However, such displacements in complex systems, and in particular a system containing a 1,3-dioxane ring, have not been successfully carried out. In point of fact, Sunay, U. and Fraser-Reid, B., Tetrahedron Letters, 27, pages 5335-5338 (1986) reported the failure of such a displacement in a system containing a 1,3-dioxane ring.

Thus, we have surprisingly and unexpectedly found that the nitrile of the present invention, (4R-cis)-1,1-dimethylethyl-6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, can be obtained by a process of displacing various activated sulfonate or halide 1,3-dioxane derivatives with a metal cyanide.

The object of the present invention is an improved, short, efficient, and economical process for the preparation of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate. Thus, the present method avoids the costly, low temperature reaction of the prior method and is amenable to large scale synthesis.

SUMMARY OF THE INVENTION

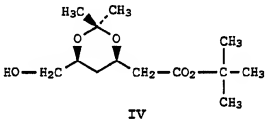
Accordingly, a first aspect of the present invention is an improved process for the preparation of the compound of Formula I



I

which comprises:

(a) treating the compound of Formula IV

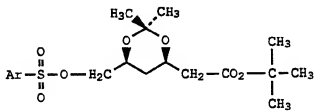


IV

with a compound of Formula V

V

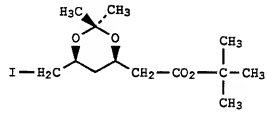
wherein Ar is aryl; and X is halogen in the presence of a base and a solvent to afford a compound of Formula II



II

wherein Ar is as defined above; or alternatively

(b) treating a compound of Formula II with an alkali iodide in a solvent at about 0°C to about the reflux temperature of the solvent to afford the compound of Formula III



III

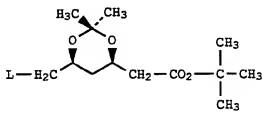
(c) treating a compound of Formula II or the compound of Formula III with a compound of Formula VI

M-CN

VI

wherein M is an alkali metal, silver or copper (I) in a solvent at about 0°C to about 100°C to afford the compound of Formula I.

A second aspect of the present invention is a novel intermediate of Formula



wherein L is halogen or  , wherein Ar is aryl,

which is useful in the preparation of the compound of Formula I

DETAILED DESCRIPTION OF THE INVENTION

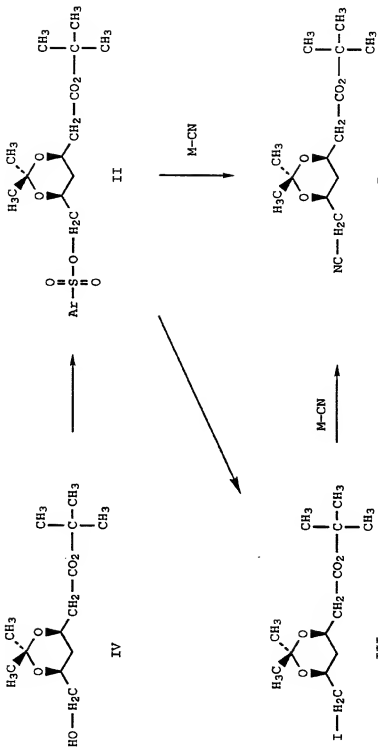
In this invention, the term "aryl" means an aromatic radical which is a phenyl group substituted by one to two substituents selected from halogen or nitro.

"Halogen" is iodine, bromine, chlorine, and fluorine.

"Alkali metal" is a metal in Group IA of the periodic table and includes, for example, lithium, sodium, potassium, and the like.

The process of the present invention is a new, improved, economical, and commercially feasible method for preparing (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate. The process of the present invention is outlined in the following scheme:

SCHEME I



A compound of Formula II wherein Ar is aryl is prepared by treating the compound of Formula IV with a compound of Formula V

V

wherein X is a halogen such as, for example, chlorine, bromine, iodine, fluorine, and the like, and Ar is as defined above in the presence of a base such as, for example, triethylamine, diisopropylethylamine, 4-dimethylaminopyridine and the like, and a solvent such as, for example, pyridine, toluene, methylene chloride, and the like at about 0°C to about 40°C to afford a compound of Formula II. Preferably the reaction is carried out in the presence of triethylamine in methylene chloride at about 0°C to about 25°C.

The compound of Formula III is prepared by treating a compound of Formula II with an alkali iodide such as, for example, sodium iodide, potassium iodide, and the like in a solvent such as, for example, acetone, 2-butanone, and the like, at about 0°C to about the reflux temperature of the solvent to afford the compound of Formula III. Preferably the reaction is carried out with sodium iodide in 2-butanone at about 55°C.

The compound of Formula I is prepared by treating either a compound of Formula II, or a compound of Formula III with a compound of Formula VI

M-CN

VI

wherein M is an alkali metal, such as, for example, lithium, sodium, potassium and the like, silver or copper (I) (cuprous) optionally in the presence of a quaternary ammonium salt such as, for example, tetrabutylammonium bromide, tetrabutylammonium iodide, benzyltriethylammonium chloride and the like in a solvent such as, for example, ethanol, dimethyl sulfoxide, dimethylformamide, dimethylpropyleneurea, dimethylethyleneurea, tetramethylurea, N-methylpyrrolidinone, tetrahydrofuran, toluene, methylene chloride, and the like, mixtures thereof, as well as any of the aforementioned water-immiscible solvents in combination with water, that is, in a phase transfer procedure using the quaternary ammonium salts as described above at about 0°C to about the reflux temperature of the solvent to afford a compound of Formula I. Preferably the reaction is carried out in dimethyl sulfoxide at about 20°C to about 50°C.

The compound of Formula IV is disclosed in European Patent Application 0 319 847. Compounds of Formula V and Formula VI are either known or capable of being prepared by methods known in the art.

Copending United States Patent Application Serial Number 303,733 discloses the use of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate in the preparation of (4R-cis)-1,1-dimethylethyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, which in turn is used to prepare (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-

yl)ethyl]-1H-pyrrole-3-carboxamide or the salt of the hydroxy acid, [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1), corresponding to the opened lactone ring of the aforementioned compound which is disclosed in United States Patents 4,647,576 and 4,681,893 as a useful hypolipidemic and hypocholesterolemic agent.

The following examples are illustrative to show the present process, the preparation of starting materials, and the use of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate obtained by the present process to prepare the key intermediate, (4R-cis)-1,1-dimethylethyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, in the synthesis of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide or the salt of the hydroxy acid, [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1), corresponding to the opened lactone ring of the aforementioned compound useful as a hypolipidemic and hypocholesterolemic agent.

EXAMPLE 1

(4R-cis)-1,1-Dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

Method A

Step A: Preparation of (4R-cis)-1,1-dimethylethyl 6-(4-bromobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring, 20-25°C solution of the (4R-cis)-1,1-dimethylethyl 6-hydroxymethyl-2,2-dimethyl-1,3-dioxane-4-acetate (European Patent Application 0319,847) (10 g, 38 mmol) in methylene chloride) (250 mL) containing triethylamine (10 mL, 72 mmol) is added 4-bromobenzenesulfonyl chloride (15 g, 57.5 mmol). Stirring is continued at 20-25°C for 20 hours, the solution is poured onto 250 mL of water and the layers separated. The upper aqueous layer is extracted with 250 mL of methylene chloride and the combined organic layers are washed with 200 mL each of saturated sodium bicarbonate solution, to ensure complete removal of 4-bromobenzenesulfonyl chloride and then saturated sodium chloride solution. Drying the solution with magnesium sulfate and concentration in vacuo gives 26.3 g of the product as a light orange solid.

Step B: Preparation of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 20-25°C solution of the crude 4-bromobenzenesulfonate (24.2 g, 36 mmol) in dimethyl sulfoxide (100 mL) is added sodium cyanide (4.0 g, 81 mmol). The mixture is stirred at 20-25°C for 42 hours, a further 2 g (40.5 mmol) of sodium cyanide is added, and stirring continued at 20-25°C for 96 hours. The mixture is poured onto 200 mL of water and extracted with 2 x 200 mL of ethyl acetate. The

combined extracts are washed with 100 mL each saturated sodium bicarbonate solution, saturated sodium chloride solution, dried (magnesium sulfate), and concentrated in vacuo to give the product, 11.3 g as a red-brown oil, which solidifies on standing. Column chromatography on flash silica gel and eluting with hexane/ethyl acetate (4:1) gives the product 9.5 g, as pale yellow needles; mp 67.2-69.7°C. Vapor phase chromatography (VPC): 30 meter DB-5 capillary column 40 to 280°C at 15°C/min. 18.63 min., 98.35% (area).

Nuclear magnetic resonance (^{1}H-NMR): ($CDCl_3$) δ 1.38 (3H, s), 1.45 (9H, s), 1.75 (1H, m), 2.39 (2H, dq), 2.51 (2H, d), 4.10-4.32 (2H, m).

Optical Rotation: $[\alpha]_D$ = 1.33° (C=1, $CHCl_3$).

Method B

Step A: Preparation of (4R-cis)-1,1-dimethylethyl 6-(4-chlorobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring, 0-5°C solution of the (4R-cis)-1,1-dimethylethyl 6-hydroxymethyl-2,2-dimethyl-1,3-dioxane-4-acetate (European Patent Application 0319,847) (10 g, 38 mmol) in methylene chloride (250 mL) containing triethylamine (10 mL, 72 mmol) is added 4-chlorobenzenesulfonyl chloride (12.7 g, 60 mmol). Stirring is continued at 0-5°C for 2.5 hours and the solution slowly warmed to 20-25°C over a period of 2 hours. The solution is poured onto 200 mL of water and the layers separated. The upper aqueous layer is extracted with 200 mL of methylene chloride and the combined organic layers are washed with 200 mL each of saturated sodium bicarbonate solution to ensure complete removal of 4-chlorobenzenesulfonyl chloride and then saturated

sodium chloride solution. Drying the solution with magnesium sulfate and concentration in vacuo gives 21.5 g of the product as a pale yellow solid.

Step B: Preparation of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 20-25°C solution of the crude 4-chlorobenzenesulfonate (21.5 g, 38 mmol) in dimethyl sulfoxide (100 mL) is added sodium cyanide (4.0 g, 81 mmol). The mixture is stirred at 20-25°C for 40 hours, a further 2 g (40.5 mmol) of sodium cyanide is added and stirring continued at 20-25°C for 4.5 hours and 48-52°C for 24 hours. The mixture is poured onto 200 mL of water and extracted with 2 x 250 mL of ethyl acetate. The combined extracts are washed with 100 mL each saturated sodium bicarbonate solution, saturated sodium chloride solution, dried (magnesium sulfate), and concentrated in vacuo to give the product, 11.7 g as a yellow-orange solid. The product is 90% pure (by VPC).

Method C

Step A: Preparation of (4R-cis)-1,1-dimethylethyl 6-(2,5-dichlorobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 0-5°C solution of the (4R-cis)-1,1-dimethylethyl 6-hydroxymethyl-2,2-dimethyl-1,3-dioxane-4-acetate (European Patent Application 0319,847) (10 g, 38 mmol) in methylene chloride (250 mL) containing triethylamine (10 mL, 72 mmol) is added 2,5-dichlorobenzenesulfonyl chloride (14.7 g, 57.5 mmol). Stirring is continued at 0-5°C for 3.5 hours, the solution is poured onto 200 mL of water, and the layers separated. The upper aqueous

layer is extracted with 200 mL of methylene chloride and the combined organic layers are washed with 200 mL each of saturated sodium bicarbonate solution to ensure complete removal of 2,5-dichlorobenzenesulfonyl chloride and then saturated sodium chloride solution. Drying the solution with magnesium sulfate and concentration in vacuo gives 24.6 g of the product as a yellow-orange oil.

Step B: Preparation of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 20-25°C solution of the crude 2,5-dichlorobenzenesulfonate (24.6 g, 38 mmol) in dimethyl sulfoxide (100 mL) is added sodium cyanide (4.0 g, 81 mmol). The mixture is stirred at 20-25°C for 44 hours, a further 1 g (20 mmol) of sodium cyanide is added and stirring continued at 20-25°C for 24 hours. The mixture is poured onto 200 mL of water and extracted with 2 x 250 mL of ethyl acetate. The combined extracts are washed with 100 mL each saturated sodium bicarbonate solution, saturated sodium chloride solution, dried (magnesium sulfate), and concentrated in vacuo to give the product, 10.7 g as a brown oil, which solidifies on standing. The material is 85% pure (by VPC).

Method D

Step A: Preparation of (4R-cis)-1,1-dimethylethyl 6-(2-nitrobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 20-25°C solution of the (4R-cis)-1,1-dimethylethyl 6-hydroxymethyl-2,2-dimethyl-1,3-dioxane-4-acetate (European Patent Application 0319,847) (10 g, 0.038 mol) in methylene chloride (250 mL) containing triethylamine (7 mL,

0.05 mol) is added 2-nitrobenzenesulfonyl chloride (9.8 g, 0.043 mol). Stirring is continued at 20-25°C for 24 hours, a further portion of 2-nitrobenzenesulfonyl chloride (2.0 g, 0.009 mol) is added and the solution stirred for a further 4 hours. The solution is then poured onto 200 mL of water and the layers separated. The upper aqueous layer is extracted with 250 mL of methylene chloride and the combined organic layers are washed with 100 mL each of saturated sodium bicarbonate solution to ensure complete removal of 2-nitrobenzenesulfonyl chloride and then saturated sodium chloride. Drying the solution with magnesium sulfate and concentration in vacuo gives 20.8 g of the product as a green oil.

Step B: Preparation of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 20-25°C solution of the crude 2-nitrobenzenesulfonate (19 g, 35.8 mmol) in dimethyl sulfoxide (100 mL) is added sodium cyanide (4.0 g, 81 mmol). The mixture is stirred at 20-25°C for 17 hours, poured onto 200 mL of water, and extracted with 2 x 200 mL of ethyl acetate. The combined extracts are washed with saturated sodium bicarbonate solution, saturated sodium chloride solution, dried (magnesium sulfate), and concentrated in vacuo to give the product, 10.8 g as a red-brown oil. Column chromatography on flash silica eluting with hexane/ethyl acetate (4:1) gives the product 8.1 g, as a yellow oil which solidifies on standing. The product is 97.4% pure (by VPC).

Method E

Step A: Preparation of (4R-cis)-1,1-dimethylethyl 6-(4-nitrobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 20-25°C solution of the (4R-cis)-1,1-dimethylethyl 6-hydroxymethyl-2,2-dimethyl-1,3- dioxane-4-acetate (European Patent Application 0319,847) (10 g, 0.038 mol) in methylene chloride (250 mL) containing triethylamine (7 mL, 0.05 mol) is added 4-nitrobenzenesulfonyl chloride (10.5 g, 43 mmol). Stirring is continued at 20-25°C for 22 hours, the solution is poured onto 200 mL of water and the layers separated. The upper aqueous layer is extracted with 250 mL of methylene chloride and the combined organic layers are washed with 100 mL each of saturated sodium bicarbonate solution to ensure complete removal of 4-nitrobenzenesulfonyl chloride and then saturated sodium chloride solution. Drying the solution with magnesium sulfate and concentration in vacuo gives 18.7 g of the product as a brown oil which solidifies immediately.

Step B: Preparation of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 40-45°C solution of the crude 4-nitrobenzenesulfonate (12.7 g, 28.5 mmol) in dimethyl sulfoxide (100 mL) is added sodium cyanide (4.0 g, 81 mmol). The mixture is stirred at 40-45°C for 1 hour, poured onto 200 mL of water and extracted with 2 x 200 mL of ethyl acetate. The combined extracts are washed with 100 mL each saturated sodium bicarbonate solution, saturated sodium chloride solution, dried (magnesium sulfate), and concentrated in vacuo to give the product, 8 g as a red-brown oil. Column chromatography on flash silica eluting with

hexane/ethyl acetate (4:1) gives the product 2.8 g as a yellow oil which solidifies on standing. The product is 98.0% pure (by VPC).

Method F

Step A: Preparation of (4R-cis)-1,1-dimethylethyl 6-(4-chlorobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring, 0-5°C solution of the (4R-cis)-1,1-dimethylethyl 6-hydroxymethyl-2,2-dimethyl-1,3-dioxane-4-acetate (European Patent Application 0319,847) (10 g, 38 mmol) in methylene chloride (250 mL) containing triethylamine (10 mL, 72 mmol) is added 4-chlorobenzenesulfonyl chloride (12.7 g, 60 mmol). Stirring is continued at 0-5°C for 2.5 hours and the solution slowly warmed to 20-25°C over a period of 2 hours. The solution is poured onto 200 mL of water and the layers separated. The upper aqueous layer is extracted with 200 mL of methylene chloride and the combined organic layers are washed with 200 mL each of saturated sodium bicarbonate solution to ensure complete removal of 4-chlorobenzenesulfonyl chloride and then saturated sodium chloride solution. Drying the solution with magnesium sulfate and concentration in vacuo gives 21.5 g of the product as a pale yellow solid.

Step B: Preparation of (4R-cis)-1,1-dimethylethyl 6-iodomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring, 55 to 60°C suspension of the (4R-cis)-1,1-dimethylethyl 6-(4-chlorobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate (21.5 g, 38 mmol) in 2-butanone (100 mL) containing potassium carbonate (10 g, 77 mmol) is added sodium iodide (11.4 g, 77 mmol). Stirring is continued at 55°C for

30 minutes. The mixture is then heated to a gentle reflux for 18 hours, the solids removed by filtration and the filtrate concentrated to give the product 14 g as an oil.

Step C: Preparation of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate

To a stirring 20 to 25°C solution of the crude iodide (14 g, 38 mmol) in dimethyl sulfoxide (150 mL) is added sodium cyanide (3.8 g, 77 mmol). The mixture is stirred at 20 to 25°C for 5 days, poured onto 300 mL water and extracted with 2 x 250 mL of ethyl acetate. The combined extracts are washed with saturated sodium bicarbonate solution, saturated sodium chloride solution, dried (magnesium sulfate), and concentrated in vacuo to give the product, 10 g as a pale-yellow oil which solidifies on standing. The product is 82.4% pure (by VPC).

EXAMPLE 2

(4R-cis)-1,1-dimethylethyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate

A solution of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, (Example 1) 5.63 g (0.048 mol), in 100 mL of methanol saturated with gaseous ammonia is treated with 0.5 g of Raney nickel #30 and hydrogen gas in a shaker at 50 pounds per square inch (psi) and 40°C. After 16 hours, thin layer chromatography indicates no starting nitrile present. The suspension is cooled, filtered through filter aid, and concentrated to an oil. This crude oil is purified by flash chromatography on silica gel with 30:20:1 (ethyl acetate:methanol:ammonium hydroxide) as eluant to give 4.93 g of (4R-cis)-1,1-dimethylethyl 6-(2-aminoethyl)-

2,2-dimethyl-1,3-dioxane-4-acetate (98.2 area %) as a clear oil.

200 MHz ^{1}H-NMR ($CDCl_3$) 1.0 - 1.2 (m, 1H), 1.22 (s, 3H), 1.31 (s, 12H), 1.35 - 1.45 (m, 3H), 2.15 (dd, 1H, J = 15.1 Hz, J = 6.2 Hz), 2.29 (dd, 1H, J = 15.1 Hz, J = 7.0 Hz), 2.66 (t, 2H, J = 6.6 Hz), 3.82 (m, 1H), 4.12 (m, 1H).

^{13}C-NMR ($CDCl_3$, 50 MHz) δ 19.60, 27.96, 30.00, 36.50, 38.25, 39.79, 42.61, 66.08, 67.18, 80.21, 98.35, 169.82.

GC/MS m/e 202, 200, 173, 158, 142, 140, 114, 113, 100, 99, 97, 72, 57.

FTIR (neat) 951.6, 1159.9, 1201.1, 1260.3, 1314.3, 1368.3, 1381.2, 1731.0, 2870.3, 2939.8, 2980.9, 3382.2 cm^{-1}.

EXAMPLE 3

(±)4-Fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,β-diphenylbenzenebutaneamide mixture of [R-(R*,R*)], [R-(R*,S*)], [S-(R*,R*)] and [S-(R*,S*)] isomers

Step A: Preparation of 4-Methyl-3-oxo-N-phenyl-2-(phenylmethylene)pentanamide

A suspension of 100 kg of 4-methyl-3-oxo-N-phenylpentanamide (Example A) in 660 kg of hexanes is treated with agitation under nitrogen with 8 kg of β-alanine, 47 kg of benzaldehyde, and 13 kg of glacial acetic acid. The resulting suspension is heated to reflux with removal of water for 20 hours. An additional 396 kg of hexanes and 3 kg of glacial acetic acid is added and reflux continued with water removal for 1 hour. The reaction mixture is cooled to 20 to 25°C, and the product is isolated by filtration. The product is purified by slurrying in hexanes at 50-60°C, cooling, and filtration. The product is

slurried twice with water at 20 to 25°C, filtered, and dried in vacuo to yield 110 kg of 4-methyl-3-oxo-N-phenyl-2-(phenylmethylene)pentanamide, mp 143.7-154.4°C.

Vapor Phase Chromatography (VPC): 30 meter DB-5 capillary column 50 to 270°C at 15°C/min. 19.33 min., 99.7% (area).

Gas Chromatography/Mass Spectrometry (GC/MC): M/Z 293 $[M]^+$.

Nuclear Magnetic Resonance (^{1}H-NMR): ($CDCl_3$) δ 1.16 (6H, d), 3.30 (1H, quin.), 7.09 (1H, m), 7.28 (5H, m), 7.49 (5H, m), 8.01 (1H, brs).

Step B: Preparation of (±)4-Fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N-ß-diphenylbenzenebutaneamide mixture of [R-(R*,R*)], [R-(R*,S*)], [S-(R*,R*)] and [S-(R*,S*)]isomers

A solution of 17.5 kg of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide in 300 L of anhydrous ethanol is concentrated by distillation of 275 L of the ethanol. Under an argon atmosphere, 100 kg (340 mol) of 4-methyl-3-oxo-N-phenyl-2-(phenylmethylene)pentamide, 47.5 L (340 mol) of triethylamine, and 40 L (375 mol) of 4-fluorobenzaldehyde are added. The resulting solution is stirred and heated at 75 to 80°C for 23 hours. The product begins to form as solid after approximately 1.5 hours but approximately 24 hours is required for essentially complete conversion. The slurry is dissolved in 600 L of isopropanol at 80°C. The resulting solution is slowly cooled and the (±)4-fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,ß-diphenyl-benzenebutaneamide mixture of [R-(R*,R*)], [R-(R*,S*)], [S-(R*,R*)]and [S-(R*,S*)] isomers isolated by filtration. Washing the precipitate with isopropanol and drying in vacuo

yielded 99 kg of (±)4-fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,ß-diphenylbenzenebutanamide mixture of [R-(R*,R*)], [R-(R*,S*)], [S-(R*,R*)], and [S-(R*,S*)] isomers; mp 206.8-207.6°C.

^{1}H-NMR: ($CDCl_3$) δ 1.03 (3H, d), 1.22 (3H, d), 2.98 (1H, quin.), 4.91 (1H, d, J = 11 Hz). 5.51 (1H, d, J = 11 Hz), 6.98-7.43 (12H, m), 8.17 (2H, dd), 9.41 (1H, brs).

High Pressure Liquid Chromatography (HPLC): (Acetonitrile:tetrahydrofuran:water) (40:25:55) Econosil $C_{18}5_{\mu}$ 25 cm 1.0 mL/min 254 nm 16.77 min 99.2% (area).

EXAMPLE 4

(2R-Trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

Method A

Step A: Preparation of (4R-cis)-1,1-dimethylethyl 6-[2[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrol-1-yl]ethyl]-2,2-dimethyl-1,3-dioxane-4-acetate

A solution of (4R-cis)-1,1-dimethylethyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, (Example 2) 1.36 g (4.97 mmol), and (±)-4-fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,ß-diphenyl-benzenebutaneamide mixture of [R-(R*,R*)], [R-(R*,S*)], [S-(R*,R*)], and [S-R*,S*)] isomers, (Example 3) 1.60 g (3.83 mmol), in 50 mL of heptane:toluene (9:1) is heated at reflux for 24 hours. The solution is cooled slightly and 15 mL of 2-propanol added. The mixture is allowed to cool to 25°C and filtered to give 1.86 g of (4R-cis)-1,1-dimethylethyl 6-[2[2-(4-fluorophenyl)-5-(1-methyl-ethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrol-1-

yl]ethyl]-2,2-dimethyl-1,3-dioxane-4-acetate as a yellow solid.

^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1 - 1.7 (m, 5H), 1.30 (s, 3H), 1.36 (s, 3H), 1.43 (s, 9H), 1.53 (d, 6H, J = 7.1 Hz), 2.23 (dd, 1H, J = 15.3 Hz, J = 6.3 Hz), 2.39 (dd, 1H, J = 15.3 Hz, J = 6.3 Hz), 3.5 - 3.9 (m, 3H), 4.0 - 4.2 (m, 2H), 6.8 - 7.3 (m, 14H).

^{13}C-NMR ($CDCl_3$, 50 MHz) δ 19.69, 21.60, 21.74, 26.12, 27.04, 28.12, 29.95, 36.05, 38.10, 40.89, 42.54, 65.92, 66.46, 80.59, 98.61, 115.00, 115.34, 115.42, 119.52, 121.78, 123.36, 126.44, 128.21, 128.31, 128.52, 128.75, 130.43, 133.01, 133.17, 134.69, 138.38, 141.47, 159.72, 164.64, 169.96.

Step B: Preparation of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

(4R-cis)-1,1-dimethylethyl 6-[2[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrol-1-yl]ethyl]2,2-dimethyl-1,3-dioxane-4-acetate, 4.37 g (6.68 mmol), is dissolved in 200 mL of tetrahydrofuran and 15 mL of 10% hydrochloric acid solution is added, and the solution is stirred for 15 hours. To this solution is added sodium hydroxide (3.6 g) and the mixture is stirred for 30 hours. The reaction is stopped by adding 150 mL of water, 90 mL of hexane, and separating the layers. The aqueous layer is acidified with dilute hydrochloric acid solution, stirred for 3 hours and extracted with 150 mL of ethyl acetate. A drop of concentrated hydrochloric acid is added to the ethyl acetate solution and the solution is allowed to stand 18 hours. The solution is concentrated in vacuo and the concentrate is redissolved in 50 mL of ethyl

acetate and treated with one drop of concentrated hydrochloric acid. The solution is stirred 2 hours, concentrated in vacuo, and dissolved in 3.0 mL of toluene. (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (3.01 g) is isolated in two crops.

Method B

A solution of (4R-cis)-1,1-dimethylethyl 6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, (Example 2) 2.56 g (9.36 mmol), and (±)-4-fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,ß-diphenylbenzenebutaneamide mixture of {R-(R*,R*)], [R-(R*,S*)], [S-(R*,R*)] and [S-(R*,S*)] isomers (Example 3), 3.00 g (7.20 mmol), in 60 mL of heptane:toluene (9:1) is heated at reflux for 24 hours. The solution is cooled and poured into 300 mL of tetrahydrofuran and 150 mL of saturated ammonium chloride in water. The layers are separated and the organic layer is added to 15 mL of 10% hydrochloric acid solution and the solution is stirred for 15 hours. To this solution is added sodium hydroxide (3.6 g) and the mixture is stirred for 30 hours. The reaction is stopped by adding 150 mL of water, 90 mL of hexane, and separating the layers. The aqueous layer is acidified with dilute hydrochloric acid solution, stirred for 3 hours and extracted with 150 mL of ethyl acetate. A drop of concentrated hydrochloric acid is added to the ethyl acetate solution and the solution is allowed to stand 18 hours. The solution is concentrated in vacuo and the concentrate is redissolved in 50 mL of ethyl acetate and treated with one drop of concentrated hydrochloric acid. The solution is stirred 2 hours, concentrated in vacuo, and dissolved in 3.0 mL of

toluene. (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (2.92 g) is isolated in two crops.

PREPARATION OF STARTING MATERIALS

EXAMPLE A

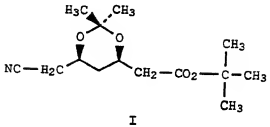
4-Methyl-3-oxo-N-phenylpentamide

A three-necked, 12-L round-bottom flask equipped with a mechanical stirrer, a thermometer, and set up for distillation is charged with 2.6 L of toluene, 1.73 kg (12 mol) of methyl 4-methyl-3-oxopentanoate and 72 g (1.18 mol) of ethylenediamine. The mixture is heated to 80°C and charged with 0.49 kg of aniline. The mixture is brought to reflux and distillation started. After 40 minutes a further 0.245 kg of aniline is charged and at 40-minute intervals a further two portions of aniline (0.245 and 0.25 kg) are charged. Distillation is continued for a further one to five hours until a total of 985 mL of solvent is removed. The solution is stirred at room temperature for 16 hours and a further 550 mL of solvent is removed by vacuum distillation (using approximately 85 mm Hg). The mixture is cooled and 2 L of water is charged to provide an oil. The mixture is warmed to 40°C and a further 1.0 L of water is charged. Seven hundred milliliters of toluene-water mixture is removed by vacuum distillation (approximately 20 mm Hg). Two liters of water is charged and the mixture is allowed to stand for 10 days. The product is isolated by filtration and washed with three portions of hexane. Drying in vacuo gives 1.7 kg of 4-methyl-3-oxo-N-phenylpentanamide as a hydrate; m.p. 46.5-58.8°C.

HPLC: 98.8% - retention time 3.56 minutes. 65/35 acetonitrile/water on a dry basis.
VPC: 87.6% - retention time 12.43 minutes, also 10.8% aniline (decomposition).

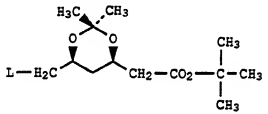
CLAIMS

1. A process for the preparation of the compound of Formula I



I

which comprises treating a compound of Formula



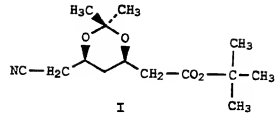
wherein L is halogen or Ar-S(=O)(=O)-O-, wherein Ar is aryl, with a compound of Formula VI

M-CN

VI

wherein M is an alkali metal, silver or copper (I) in a solvent at about 0°C to about 100°C to afford a compound of Formula I.

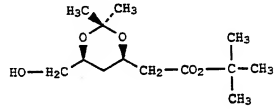
2. A process for the preparation according to Claim 1 of the compound of Formula I



I

which comprises:

Step (a) treating the compound of Formula IV

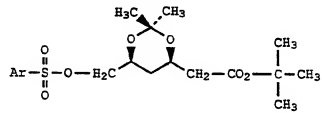


IV

with a compound of Formula V

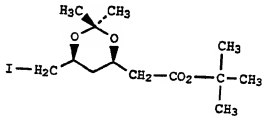
V

wherein Ar is aryl; and X is halogen in the presence of a base and a solvent to afford a compound of Formula II



II

wherein Ar is as defined above; or alternatively Step (b) treating a compound of Formula II with an alkali iodide in a solvent at about 0°C to about the reflux temperature of the solvent to afford the compound of Formula III



III

Step (c) treating a compound of Formula II or the compound of Formula III with a compound of Formula VI

M-CN

VI

wherein M is an alkali metal, silver or copper (I) in a solvent at about 0°C to about 100°C to afford the compound of Formula I.

3. A process according to Claim 2 wherein the base in Step (a) is selected from the group consisting of triethylamine, diisopropylethylamine, and 4-dimethylaminopyridine.

4. A process according to Claim 3 wherein the base is triethylamine.

5. A process according to Claim 2 wherein the solvent in Step (a) is selected from the group

consisting of pyridine, toluene, and methylene chloride.

6. A process according to Claim 5 wherein the solvent is methylene chloride.

7. A process according to Claim 2 wherein the solvent in Step (b) is selected from the group consisting of acetone and 2-butanone.

8. A process according to Claim 7 wherein the solvent is 2-butanone.

9. A process according to Claim 2 wherein the alkali iodide in Step (b) is selected from the group consisting of sodium iodide and potassium iodide.

10. A process according to Claim 9 wherein the alkali iodide is sodium iodide.

11. A process according to Claim 2 wherein a compound of Formula VI in Step (c) is selected from the group consisting of lithium cyanide, sodium cyanide, potassium cyanide, silver cyanide, and cuprous cyanide.

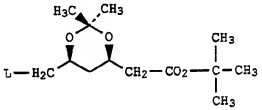
12. A process according to Claim 11 wherein the compound of Formula VI is sodium cyanide.

13. A process according to Claim 2 wherein the solvent in Step (c) is selected from the group consisting of ethanol; dimethyl sulfoxide; dimethylformamide; dimethylpropyleneurea; dimethylethyleneurea; tetramethylurea;

N-methylpyrrolidinone; tetrahydrofuran; methylene chloride; methylene chloride-water plus a quaternary ammonium salt; toluene; and toluene-water plus a quaternary ammonium salt.

14. A process according to Claim 13 wherein the solvent is dimethyl sulfoxide.

15. A compound of Formula



wherein L is halogen or  wherein Ar is aryl.

16. A compound according to Claim 4 which is selected from the group consisting of:

(4R-cis)-1,1-dimethylethyl 6-(4-bromobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate;

(4R-cis)-1,1-dimethylethyl 6-(4-chlorobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate;

(4R-cis)-1,1-dimethylethyl 6-(2,5-dichlorobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate;

(4R-cis)-1,1-dimethylethyl 6-(2-nitrobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate;

(4R-cis)-1,1-dimethylethyl 6-(4-nitrobenzene)sulfonyloxy-2,2-dimethyl-1,3-dioxane-4-acetate; and

(4R-cis)-1,1-dimethylethyl 6-iodomethyl-2,2-dimethyl-1,3-dioxane-4-acetate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/06697

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 319/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP, A2, 0330172 (WARNER-LAMBERT COMPANY) 30 August 1989, see pages 1-6, 15-16, 43 --	1-16
X,P	EP, A2, 0414206 (SHIONOGI & CO., LTD.) 27 February 1991, see page 5 formula III and page 10 --	15-16
A,P	EP, A1, 0418648 (HOECHST AKTIENGESELLSCHAFT) 27 March 1991, see page 16 formula IV -- --------	15

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th February 1992	20. 02. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme. M. van der Drift

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 91/06697

SA 52958

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/10/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0330172	30/08/89	AU-D-	3349689	06/09/89
		EP-A-	0448552	02/10/91
		JP-T-	3502798	27/06/91
		US-A-	5003080	26/03/91
		WO-A-	89/07598	24/08/89
EP-A2- 0414206	27/02/91	JP-A-	3215452	20/09/91
EP-A1- 0418648	27/03/91	AU-D-	6227790	14/03/91
		DE-A-	3929913	04/04/91
		JP-A-	3099075	24/04/91